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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,278	HARVEY	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2/20/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. Claim 43 is objected to because it recites "FACS", which should be changed to "fluorescence activated cell sorting" at the first occurrence in the claims. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining a bacterium comprising a nucleic acid sequence encoding a candidate binding polypeptide (defined as an antibody) having specific affinity for a target ligand as defined as antibodies, enabling for polypeptides that are anchored to the outer side of the inner membrane of a gram negative bacterium comprising transmembrane proteins as anchor sequences and enabling for inner membrane lipoprotein which are used as anchor sequences does not reasonably provide enablement for transmembrane protein fragments or inner membrane lipoprotein fragments used as anchor sequences.

The specification teaches that the candidate binding polypeptide of the invention can be anchored to any inner membrane lipoproteins (page 17). The

specification teaches that it has been reported that by changing amino acid 2 of lipoproteins to an arginine residue will target the lipoproteins to reside in the inner membrane (page 18). The specification teaches that all lipoproteins in *E. coli* can be anchor sequences (page 18). The specification teaches that any transmembrane loop of any cytoplasmic protein can be used as a membrane anchor (page 18). Although the specification teaches that the anchor sequences require a signal sequence and an arginine at amino acid 2 position, the specification fails to teach, what amino acids are involved in the transmembrane fragments or inner lipoproteins fragments (page 13).

There is no guidance provided as to which amino acids can be deleted and still have the protein retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally

what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such proteins.

Thomas E. Creighton, in his book, *"Proteins: Structures and Molecular Properties, 1984"*, (page 315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed

mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991"* (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to transmembrane protein fragments or inner lipoprotein fragments having claimed

functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make transmembrane protein fragments or inner lipoprotein fragments in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

3. Claims 1-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining a gram-negative bacterium comprising a nucleic acid sequence encoding a binding polypeptide having specific affinity for a target ligand comprising the steps of providing a gram-negative bacterium comprising an inner and an outer membrane and a periplasm, said bacterium expressing a nucleic acid sequence encoding a candidate binding polypeptide, wherein said candidate binding polypeptide is exposed within the periplasm of said bacterium; contacting said bacterium with a labeled ligand under conditions wherein the labeled ligand is capable of contacting the binding polypeptide, washing out unbound labeled ligand and selecting the bacterium based on the presence of the labeled ligand bound to said candidate binding polypeptide and a method of obtaining a bacterium comprising a nucleic acid sequence encoding *Fusarium solani* lipase cutinase wherein the labeled ligand is capable of diffusing into said bacterium, wherein the labeled ligands are Fluorescien dibutyrate or LysoSenor Green DND-189 (LSG) and selecting the bacterium based on the presence of the labeled ligand in the bacterium does not reasonably provide enablement providing a method of obtaining a gram-negative bacterium comprising a nucleic acid sequence encoding any candidate binding protein, contacting said bacterium with any labeled ligand under conditions wherein the labeled ligand is capable of contacting the binding polypeptide and selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification has not provided enablement for a method in the absence of a wash step in the claimed method that would enable one skilled in the art to select bacterium based on the presence of the labeled ligand in the bacterium and the use of nucleic acids as ligands.

Claims 1-47 are drawn the candidate binding polypeptide embodiment, the claimed method requires "...selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide. How would one of skill in the art distinguish between the labeled ligand bound to the candidate binding protein, verses the labeled ligand present but not bound to the protein ? There is no wash step recited in the claimed method to remove the labeled ligand bound to the candidate binding protein or labeled ligand present but not bound to the protein from the bacterium so that one of skill in the art could distinguish between the bound candidate binding protein and that which is unbound. The mere presence of labeled ligand is not a distinguishing factor.

The claimed method recites ... "wherein the labeled ligand is selected from the group consisting of a peptide, a polypeptide, an enzyme, a nucleic acid, a small molecule or a synthetic molecule". The specification teaches that methods are employed for increasing the permeability of the outer membrane to one or more labeled ligand (page 15). The specification teaches that hydrophobic antibiotics larger than 650 DA exclusion limit can diffuse through the

bacterial outer membrane itself, independent of membrane porins (page 15.) The specification teaches that the inventors have noticed that treatments such as hyperosmotic shock can improve labeling significantly (page 16).

The specification teaches in Example 13, the detection of oligonucleotide probes by antibodies expressed in the *E. coli* periplasm (page 60). Example 8 shows that the modified oligonucleotides can diffuse through the outer membrane of bacteria. Example 8 teaches that digoxigenin moiety of the oligonucleotide can be recognized by scFv antibodies specific to digoxin (anti-digoxin scFv). Example 8 teaches that cells displaying the anti-digoxin scFv antibody became clearly labeled with both digoxigenin-BODIPY™ as well as with 5-A-FL. The molecular weight of digoxigenin-BODIPY™ is 485.5 Da and the molecular weight of digoxin is 780 Da. The specification also teaches that fluorescent substrates can be used to specifically label *E. coli* cells displaying the relevant enzymes in their periplasm (Example 14, page 61). Example 9 teaches that the ability to discriminate cells expressing cutinase from control cells was determined using two different commercially available substrates, one of which is fluorescein dibutyrate which has a molecular weight of about 248 Da. The specification merely teaches that treatments such as hyperosmotic shock can improve labeling significantly. The specification teaches that known agents such as calcium ions alter the permeability of the outer membrane (page 16). However, the specification fails to teach that such altered permeability provided for the "diffusion" of all labeled ligands.

The specification does not teach that candidate binding proteins of a molecular weight greater than the exclusion limit of about 650 Da to about 900 Da can cross and enter into the periplasm or cytoplasm of a gram-negative bacteria cell without facilitated transport (i.e. diffusion). The specification fail to enable the use of all "labeled ligands", particularly those that have a molecular weight of above 2000 Da.

The teachings of the prior art regarding gram-negative transport systems, exclusion limit of molecules to cross the outer membrane and inner and outer membrane permeability are cited below:

Ames *(Journal of Bioenergetics and Biomembranes, Feb., 1988, 20(1) 1-17)* teaches that bacterial periplasmic transport systems are complex, multicomponent permeases present in gram-negative bacteria. Ames teaches that a general overall structure for bacterial transport systems is that they consists of four proteins, one of which is a soluble periplasmic protein that binds the substrate and the other three are membrane bound (see the Abstract). Ames et al teach that the liganded periplasmic protein interacts with the membrane components, which presumably form a complex and which by a series of conformational changes allow the formation of an entry pathway for the substrate (see the Abstract). Ames et al teach that the cell wall proper is commonly regarded as a widely open entirely permeable layer which confers rigidity and through which nutrients diffuse readily and the cytoplasmic membrane is imperable to almost every solute unless a special transport system is provided (page 2). Ames teaches that transport systems response to physical

treatment and osmotic shock (page 2). Decad et al, *(Journal of Bacteriology, October 1976, 128(1):325-36)* teach that the permeability function cell wall of gram-negative bacteria was investigated by producing cells with an expanded periplasmic volume and incubating them with radioactive non-utilizable oligosaccharides and polysaccharides or polyethylene glycols. Decad et al teach that only disaccharides and trisaccharides could fully diffuse into the periplasm, whereas higher molecular weight saccharides were non-penetrable. Decad et al teach that the cell wall acts as a molecular sieve with an exclusion limit near 550 to 650 daltons for saccharides (see the Abstract). Nakae et al *(The Journal of Biological Chemistry, Vo. 250, No.18, September,1975)* teach that the both the outer membrane and the peptiodoglycan layer of gram-negative bacteria acts as a barrier of the molecular sieve type for the penetration of uncharged saccharides (see the Abstract). Nakae et al teach that the exclusion limit for *E. coli* and *Salmonella typhimurium* is about 900 daltons or less for saccharides which is much smaller in comparison to gram-positive bacteria which is about 100,000 daltons for *Bacillus megaterium* (page 7363). Higgins et al *(Journal of Bioenergetics and Biomembranes, Vol. 22., No.4, 1990)* teach that bacterial binding protein-dependent transport systems are the best characterized members of the superfamily of transporters which are structurally, functionally and evolutionary related to each other (see the Abstract). Higgins et al also teach that any single system is relatively specific, different systems handle very different substrates which can be inorganic ions, amino acids, sugars, large polysaccharides or even proteins (see the Abstract). Higgins et al teach that the

distinction between binding protein-dependent transport systems and other bacterial transporters is based on two criteria: a) sensitivity to cold osmotic shock and b) differential sensitivity to metabolic inhibitors. Higgins et al teach that sensitivity of binding protein-dependent transport systems to osmotic shock is due to the loss of an essential protein component of the transport system, normally located in the periplasm between the cytoplasmic (inner) and outer membranes (pages 571-572). Higgins et al teach that in addition to the periplasmic substrate-binding protein each transport system requires a distinct complex of proteins associated with the cytoplasmic-membrane and the periplasmic binding protein delivers substrate to this protein complex, which in turn mediates its translocation across the membrane (page 572).

The prior art teaches that any single binding protein dependent system is relatively specific, different systems handle very different substrates and periplasmic substrate-binding proteins of each transport system requires a distinct complex of proteins associated with the cytoplasmic-membrane. The prior art teaches that the periplasmic binding protein delivers substrate to this protein complex, which in turn mediates its translocation across the membrane. The prior art teaches that non-facilitated transfer (i.e. diffusion) of compounds across the outer membrane has an exclusion limit of about 650 to about 900 daltons. The prior art also teaches that bacterial transport systems are sensitive to osmotic shock and physical treatment which rids the transport systems of an essential protein component which is located in the periplasm. The prior art further teaches that facilitated transport such physical treatment or osmotic shock

can induce permabilization of the gram-negative outer membrane. Webster's Ninth New Collegiate Dictionary, 1990 defines "diffusion" as the process by which particles of liquids, gases or solids intermingle as the result of their spontaneous movement caused by thermal agitation in dissolved substances move from a region of higher to one of lower concentration" (page 354).

Free diffusion (spontaneous movement) into the cytosol of a bacterium using a labeled ligand cannot be achieved. The specification has not described which ligands can be used with which transport systems? How would hydrophilic molecules (i.e. peptides, polypeptides, enzymes or nucleic acid molecules) of greater than the exclusion limit for gram negative bacteria cross the outer membrane and be translocated across the bacterium's hydrophobic cytoplasmic membrane without facilitated transport? How can peptides, polypeptides, enzymes or nucleic acid molecules) of greater than about 2000 daltons be diffused into the interior of the cell if they cannot diffuse across the outer membrane of the bacterium?

Dependent claim 22 recites "... the method of claim 1 wherein said ligand comprises a nucleic acid." If a nucleic acid is diffused into a bacterial cell which already contains a diverse array of nucleic acid molecules, how would one skilled in the art distinguish between the nucleic acid molecules that hybridize to the nucleic acid molecules of the bacterium and a candidate binding protein that binds the labeled ligand? Nucleic acid molecules are hydrophilic molecules, how can these hydrophilic molecules cross the hydrophobic cytoplasmic membrane by mere diffusion?

Claims 1-47 are drawn to the binding polypeptide embodiment of the claimed method. The specification has not shown the use of any enzymes and labeled ligands other than *Fusarium solani* lipase cutinase and the labeled ligands are Fluorescien dibutyrate or LysoSenor Green DND-189 (LSG). The specification has not shown that any peptides, polypeptides, enzymes other then *Fusarium solani* lipase cutinase and nucleic acids can cross the outer membrane. The prior art above has taught that any single binding protein dependent system is relatively specific, different systems handle very different substrates and periplasmic substrate-binding proteins of each transport system requires a distinct complex of proteins associated with the cytoplasmic-membrane. Therefore, how can peptides, polypeptides, enzymes other than *Fusarium solani* lipase cutinase and nucleic acids cross the outer membrane? Fluorescien dibutyrate and LysoSenor Green DND-189 (LSG) are known in the art to cross the inner membrane of a bacterium. However, the prior art as cited above teaches that non-facilitated transfer (i.e. diffusion) of compounds across the outer membrane has an exclusion limit of about 650 to about 900 daltons. Applicants have not described ligands other than Fluorescien dibutyrate and LysoSenor Green DND-189 that can cross the inner membrane of the bacterium. Webster's Ninth New Collegiate Dictionary, 1990 defines "diffusion" as the process by which particles of liquids, gases or solids intermingle as the result of their spontaneous movement caused by thermal agitation in dissolved substances move from a region of higher to one of lower concentration" (page 354). Free diffusion into the cytosol of a bacterium using labeled ligands other

than Fluorescien dibutyrate and LysoSenor Green DND-189 cannot necessarily be achieved. What other ligands can be used? What transport systems are used? How can peptides, polypeptides, enzymes or nucleic acid molecules, small molecules or synthetic molecules) of greater than the exclusion limit for gram-negative bacteria be diffused into the interior of the cell if they cannot diffuse across the outer membrane of the bacterium? How would hydrophilic molecules (i.e. peptides, polypeptides, enzymes, nucleic acid molecule, small molecules or synthetic molecules) greater than about 2000 Da cross the outer membrane and be translocated across the bacterium's hydrophobic cytoplasmic membrane without facilitated transport?

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The specification has failed to enable a method of obtaining a gram-negative bacterium comprising a nucleic acid sequence encoding any candidate binding protein, wherein said candidate binding protein is exposed within the periplasm of said bacterium, contacting said bacterium with any labeled ligand capable of contacting the binding polypeptide, wherein the ligand is greater than the exclusion limit for gram-negative bacteria and selecting said bacterium based

on the presence of said labeled ligand bound to said candidate binding polypeptide. It is determine that there are limited working examples commensurate in scope with the instant claims and there is limited guidance provided in the specification as to how to use the claimed method. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3 and 24 recite the term "capable of". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "capable of" cannot be ascertained. Clarification as to the meaning of this term is required.

5. Claims 1 and 43 recite the term "under conditions". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "under conditions" cannot be ascertained. Clarification as to the meaning of this term is required.

6. Claim 12 recites the term "obtained by". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "obtained by" cannot be ascertained. Clarification as to the meaning of this term is required.

7. Claim 22 recite the term "small molecule" and " synthetic molecule". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "small molecule" and " synthetic molecule" are not disclosed in the instant specification and therefore cannot be ascertained. Clarification as to the meaning of this terms is required.

8. Claims 1-47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no wash step recited in the claimed method to remove the labeled ligand bound to the candidate binding protein or labeled ligand present but not bound to the protein from the bacterium so that one of skill in the art could distinguish between the bound candidate binding protein and that which is unbound. The mere presence of labeled ligand is not a distinguishing factor.

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Vanessa L. Ford
Biotechnology Patent Examiner
April 5, 2004

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